EFFECTIVENESS OF THE TREATMENT OF DEGENERATIVE JOINT DISEASE WITH PERIARTICULAR, INTRAARTICULAR, AND INTRAMUSCULAR INJECTIONS OF ZEEL T

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Summary

Effectiveness of the treatment of degenerative joint disease by Zeel injections was assessed on the basis of published work and our own experience, including the results of a study carried out in a group of 523 patients. The solution was injected into the affected joints, periarticularly and intramuscularly. We also assessed the product's tolerability. Women were predominant (71%) in the study group. The duration of the disease varied between 1 and 10 years, with an average of 5 years. The condition was diagnosed in the knees (53%), vertebrae (30%), hips (29%), shoulders (13%), fingers (7%), tarsal joints (6%), and other joints (5%). The first signs of regression of the symptoms were noted in approximately 2/3 of the patients already after 6 injections, and after 10 injections a considerable improvement was observed in 94% of the cases. The results of the treatment were rated as very good, good, or satisfactory both by doctors and patients.

Degenerative joint disease is characterized by pathological alterations having a very diverse clinical picture. Degeneration and wasting occur in the articular cartilage, and changes in the subcartilaginous layer of bone and in the soft tissues [13]. The condition is generally accompanied by inflammatory changes in the inner layer of the articular capsule due to the infiltration of inflammatory cells (neutrophils and monocytes) and the release of free metabolites of oxygen and inflammatory cytokines [19].

The degenerative process of the hard tissues begins with non-inflammatory alterations in the articular cartilage and bone, and particularly in the subcartilaginous layer. The degenerated synovial villi still produce articular fluid, but this no longer plays its nutritional role with respect to cartilage. The latter then relatively quickly undergoes certain regressive changes, which degrade its biological and mechanical quality [14].

Degenerative joint disease is a usually painful condition that develops in all persons over the age of 65 and in approximately 2% of the whole adult population [18]. According to Bjelle [1], it is the second most frequent chronic condition in Europe. The reasons for the steadily growing number of osteoarthritis sufferers are sought in modern lifestyle, especially in the industrialized countries – for example in insufficient

exercise, unhealthy eating habits, and obesity, as has been emphasized by Krebs [11]. According to Wagenhauser [14], osteoarthritis constitutes a serious economic problem for society, accounting, in Germany, for 50 million days lost to sick leave. In 1972 osteoarthritis was diagnosed in Germany in approximately 17 million individuals, and therapeutic agents were used about 20 million times [32]. Again according to Krebs, “Rheumatism has become the most expensive disease in the industrialized world.”

Degenerative and inflammatory conditions of the musculoskeletal system are the principal cause of invalidity in the United States [13] and are the second most common cause of invalidity in Europe [32]. For example, osteoarthritis of the knee is encountered in some 2 to 18% of the population [12, 18], and according to Felson et al. [3] and to Hadler [9] it affects around 10% of all persons over the age of 65. In women the condition develops more often as a result of excessive stresses of various etiology (75%), while in men a traumatic background is predominant [13].

According to Weiser and Metelmann [32], 81% of the patients examined were aged over 50, and 61.2% of them were women. These data confirm that osteoarthritis is largely a disease of old age, particularly in women. The above authors believe that the disease is caused by age-dependent degeneration of the cartilage due to poor vascularization of the subcartilaginous layer and also by regressive aging processes leading to a progressive loss of elasticity in cartilage and in the subcartilaginous bone layer. In women a major part is also played by the hormonal changes that accompany menopause. In 82% of the cases the doctors cited as the causes of osteoarthritis the changes associated with tissue wear and endogenous disturbances.

Even though degenerative joint disease usually develops at a more advanced age, clinicians report an increasing incidence of this diagnosis in the young population [20]. This leads to a considerable impairment of musculoskeletal function and consequently to a restriction of possibilities in daily life and in occupational activity, a fact of major significance to the working population.

Treatment of degenerative joint conditions presents a number of problems and is not always successful [20]. Conditions of this kind are as a rule treated with drugs and sometimes also by various forms of kinesitherapy and physiotherapy. The pharmacological treatment consists of a temporary use of glucocorticoids, usually in the form of intraarticular or periarticular blockade. Doctors specializing in various disciplines commonly prescribe non-steroidal antiinflammatories for prolonged periods. These drugs act on the pain, inflammation, and exudation by inhibiting prostaglandin and leukotriene synthesis. Unfortunately, neither NSAIDs nor steroids promote regeneration of articular cartilage [20]. Apart from this, the use of these drugs is associated with a serious risk of the development of undesirable side effects such as irritation or damage to the digestive tract [8].

The need for the use of drugs having few side effects and yet promoting tissue regeneration biologically has resulted in increasing attention being paid by doctors to antihomotoxic preparations. A trial has thus been undertaken of the therapeutic efficacy of the product Zeel (manufactured by Biologische Heilmittel Heel GmbH,

Germany) injected intraarticularly or periarticularly in degenerative conditions of the musculoskeletal system.

To ensure normal articular function a balance must be maintained between the metabolic processes taking place in the synovial membrane and in the articular cartilage [20, 32, 34]. Within the cartilage lactic acid is formed, which is transported by articular fluid to parietal cells of the articular capsule. There energy is released in processes of the tricarboxylic acid cycle [5].

In degenerative joint disease certain disturbances of metabolic processes occurring within the joint, i.e. within the cartilage, the synovial membrane, and synovial fluid, lead to increased breakdown of connective-tissue structures. Catabolic processes thus begin to predominate over anabolic. The fundamental reaction acting as a source of energy is the formation of a hydrogen molecule which is then taken up by a molecule of nicotinamide adenine dinucleotide (NAD). All hydrogen liberated in the tricarboxylic acid cycle reacts with NAD, constituting the first link in the respiratory chain. The reaction between lactic and pyruvic acids, catalysed by NAD, is of decisive importance for the metabolism of articular tissues [5]. J. Gawęda and R. Duda report that another compound acting as a hydrogen carrier and at the same time a coenzyme engaged in the process of oxidative decarboxylation (conversion of pyruvic acid into a so-called active acetate) is α-lipoic acid. With participation of coenzyme A an active acetate may be formed, which acts as ‘ignition’ for the tricarboxylic acid cycle. On the other hand, the role of oxaloacetate may be described as a ‘fuel’ or ‘drive’ of this cycle [5].

The objective of treatment with Zeel is restoration of physiological relationships in pathologically altered joints. This is achieved by promotion of anabolic processes and simultaneous inhibition of the catabolic ones [32].

The organ extracts contained in Zeel (Cartilago suis, Funiculus umbilicalis suis) serve as important structural material for connective tissue. Placenta suis promotes blood flow and Embryo suis has general stimulating activity. The constituents of plant origin (Rhus toxicodendron, Dulcamara, Sanguinaria, Symphytum, Arnica) are used in the treatment of rheumatic diseases, especially in those cases in which the complaints are aggravated by humidity [5].

According to Gawęda and Duda, Zeel T is a highly valuable pharmacological combination of active and non-toxic homeopathic agents. Its efficacy in articular diseases has been confirmed in clinical trials and by the latest biochemical studies. The composition of Zeel is decisive for its therapeutic value [2, 4-7, 10, 14, 15, 18, 20-23, 30, 32, 34, 35]. In our own work we conducted observations on the efficacy of Zeel T injected into the joints of osteoarthritis patients.

Material

The inclusion criterion for this study was diagnosis of a degenerative joint condition manifested by pain and functional impairment and confirmed by changes discernible in the radiological picture.

The observations were carried out on 523 patients diagnosed with osteoarthritis. The largest group in this population was represented by osteoarthritis of the knee joints (53%). This was followed in descending order by osteoarthritis in the vertebral joints (30%), hip joints (29%), shoulders (13%), fingers (7%), tarsal joints (6%), and other (5%). Women were predominant (71%) (Table 1). Since the condition is chronic, the patients were as a rule over 50, the largest age group being 61-70 (32%).

Table 1: Localization of the changes in degenerative joint disease in the group of 523 patients

Localization of the changes	No. of cases	Percentage
Knee joints	279	53.0
Vertebral joints	158	30.0
Hip joints	151	29.0
Shoulder joints	67	13.0
Finger joints	39	7.0
Tarsal joints	31	6.0
Other	28	5.0
Total	753	

The most important risk factor was found to be excess weight (46%). There was no clear difference in the case of persons engaged in physical labor that could have led to overloading of the musculoskeletal system. According to our observations, therefore, the patients' occupation did not have any significant influence. In only 16% of the cases had the condition been present for less than 6 months. The characteristic clinical signs, such as articular pain, restriction of mobility, loss of strength in muscles acting on the joint, joint deformation, and changes in articular cartilage, the subcartilaginous bone layer, and the synovial membrane were generally found in patients in whom the osteoarthritis had been present for longer than 6 months.

The greatest number of patients with the above-mentioned complaints (38%) had a history of osteoarthritis longer than 5 years. Changes in cartilage and in the subcartilaginous bone layer were most frequent (56%); these were due to various kinds of internal damage (47%), secondary joint deformation (12%), congenital developmental abnormalities (4%), and other causes (15%).

Typical treatment had been used in 88% of the patients. Most of them (57%) had been given combined treatment, i.e. both drugs and therapeutic rehabilitation. The medication consisted most often of non-steroidal antiinflammatories (NSAIDs) (75%), corticosteroids (14%), cartilage-protecting agents (12%), and other drugs (14%).

In 53% of the cases the affected joints were inflamed. Articular pain was present in 95% of them, exudation in 28%, excessive heat in 27%, reddening of the skin in 7%, and other symptoms (such as instability of the joint, deformation, etc.) in 13%. The characteristic symptoms of osteoarthritis, such as impairment of mobility, incipient pain, pain during exercise, and constant pain developed with time in 96% of the patients.

The exclusion criteria were age below 30 or over 85 years, osteoarthritis caused by a comparatively recent trauma or recent infection in the joint (less than 12 months earlier), exacerbation of the inflammatory reaction causing excessive intensification of the above-mentioned symptoms, qualification for surgical treatment of the joint, history of sensitivity to Zeel, serious diseases of the liver or kidneys, and immunosuppressive therapy during the preceding month.

Methods

The preparation was introduced into the individual joints by injection. Various doses were used, depending on the size of the joint: 2 ampoules at a time in the case of large joints such as the knees, 1 ampoule into medium (e.g., tarsal) joints, and half to a quarter of an ampoule into small (e.g., interphalangeal) joints.

The injections were given twice a week, and the entire course of treatment did not exceed 10 injections. Apart from intraarticular injections (36% of the patients), we used the periarticular (30%) and intramuscular (34%) routes. Additional treatment was also prescribed in 85% of the cases. In most of them (51%) this was pharmacological therapy (30%) and physiotherapy (17%). Pharmacotherapy was conducted in two versions, using Zeel in tablets and ointments (62%) and NSAIDs (35%). The duration of treatment ranged from 2 to 6 weeks.

Results

The observations showed that an improvement consisting of a regression of the complaints, and above all of pain, became perceptible after 4-7 injections, most often after 6. Such improvement was documented in two-thirds of the patients studied. In the remaining cases most of the pathological symptoms regressed after 10 injections. A distinct improvement was thus noted in 94% of the cases.

Depending on the degree of improvement, the patients were divided into the following treatment outcome groups: very good result (12%), good (53%), satisfactory (29%); the remaining 6% comprised patients with no improvement or with a deterioration (Fig. 1).

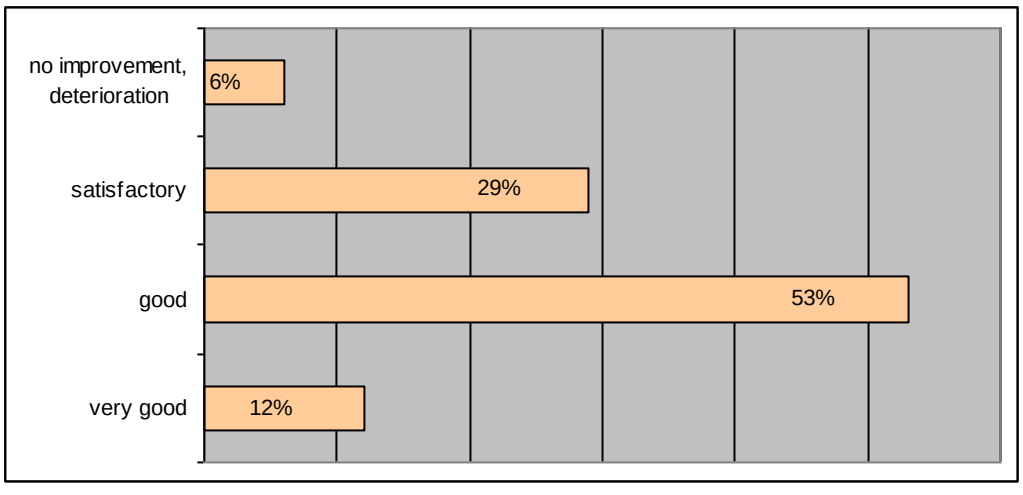

Fig. 1: Assessment of treatment outcomes

Complications occurred in 14 patients, in the form of local adverse reactions to the Zeel T injection: pain around the site of injection, hot, reddened, and itching skin, exudation into the joint, edema of the soft tissues, and also punctiform extravasations and eczema. In addition to this, 1 patient reported headache and nausea, and 1 other an elevated temperature and facial flush.

Discussion

Toxic substances – both exogenous, originating outside the human organism, and endogenous – provoking reactions of the major defense system are referred to as homotoxins. The reaction of the defense system consists of neutralization of homotoxins that cause the development of disease. This neutralization takes place in the following systems:

- in the reticuloendothelial system, which is responsible for humoral (acquired) resistance and where the toxins are stored and antibodies produced;
- in the pituitary-adrenal system and connective tissue, with which are associated the resistance mechanisms regulating the excitation and inhibition of inflammatory reactions;
- through regulation of neural movement resistance (excitation and inhibition system) with the aid of neural therapy, acupuncture, physiotherapy, massage, etc.;
- in the liver, owing to its detoxification function consisting of binding of the homotoxins by acids, their storage, and utilization of the properdin system, one of the fundamental though non-specific elements of the organism's response to infection;
- in mesenchymal connective tissue, in which too the homotoxins are stored, where the reactions of antigen and leucocyte formation take place, and where the inflammation process leads to increased phagocyte activity and to greater numbers and increased activity of immunologically active lymphocytes [5].

The human organism eliminates homotoxins from circulation, collecting them at first in the matrix (deposition phase) and subsequently, in higher concentrations, in individual tissues (impregnation phase), after which the homotoxins lead to tissue degeneration (degeneration phase). The cells become increasingly defenseless against the homotoxins, which threatens the organization of their genetic information and leads to metabolic disturbances. This may result in a change from their earlier form and function (dedifferentiation phase). It follows that condensation of homotoxins is the most important problem in controlling tissue pathology, including also the changes that take place in the course of degenerative diseases [5]. Antihomotoxic biotherapeutic preparations displace the phase of homotoxicosis in the direction of the physiological phase of elimination, which results in detoxification of the system and functional compensation at the site of damage caused by the homotoxins.

Among the many medicinal products made by Heel and used in antihomotoxic therapy of musculoskeletal pathology, the different galenic forms of Zeel play an important part, perhaps even a key part, in the treatment of degenerative disease. Podbiełkowski and Nejman [20] have listed the individual constituents of Zeel

injection solution. The constituents of plant origin are Rhus toxicodendron (poison ivy), Dulcamara (woody nightshade), Sanguinaria (bloodroot), Symphytum (common comfrey), and Arnica montana (arnica). These have a recognized activity in rheumatic and degenerative conditions, and they have long been used in exacerbation episodes, particularly in a cold and wet environment.

One very important constituent of Zeel is sulfur, long known as an effective therapeutic agent and today used especially under sanatorium conditions. Sulfur is a constituent of all kinds of human proteins and mucopolysaccharides. On account of its absorptive properties it is often used in inflammatory conditions associated with exudation. It also reduces the passive congestion responsible for the persistent pains in degenerative diseases and potentiates the action of other agents.

Acidum silicicum colloidale (colloidal silicic acid anhydride) acts on bone tissue, connective tissue, and nerve tissue, improving mechanical strength and functionality of tendons and bones.

In addition to the above-mentioned constituents of plant origin, sulfur, and silicic acid, Zeel contains coenzymes and constituents of animal origin.

The latter are as follows: Cartilago suis (pig cartilage), which strengthens articular cartilage and bone, Funiculus umbilicalis suis (pig umbilical cord), Placenta suis (pig placenta), and Embryo suis (pig embryo). The last three of these constituents improve blood flow in tissues, support normal connective tissue function, and stimulate metabolic processes.

The coenzymes present in Zeel include nadide, which stimulates oxidation processes, coenzyme A, which plays an important part in the tricarboxylic acid cycle, and thioctic acid, which is involved in the transformation of pyruvic acid. Another constituent active in the tricarboxylic acid cycle and in redox processes is sodium oxaloacetate.

Thanks to the above-mentioned constituents Zeel regulates the composition of articular fluid and synovial membrane metabolism and in addition exerts a protective and regenerative action on articular cartilage. This is particularly important in osteoarthritis, in which pathological alterations affect various biological structures of the joint. Zeel also corrects the balance between catabolic and anabolic processes. As a result of all these properties, the preparation has an analgesic, antiinflammatory, and certain antiexudative action [20, 32, 35].

As has already been said in the introduction, osteoarthritis is a disease encountered especially in old age, and more often in women than in men. In these cases the causes are age-dependent degenerative changes due to poor vascularization. With advancing age there is a loss of elasticity in cartilage and in the subcartilaginous bone layer. In time the degenerative changes advance to a considerable extent into the subcartilaginous bone layer, leading to a disturbance of venous circulation and hyperemia of the bone marrow. This increases the intramarrow pressure in the subcartilaginous layer, and the resulting compression of interosseous nerve fibers due to increased interosseous pressure gives rise to pain. This has been described by Helal in 1965 and by Arnoldi in 1978 [14, 32]. The degenerating synovial villi now

produce articular fluid that is no longer capable of performing its nutritional function. The net result is that the synovial membrane undergoes regressive changes relatively early, losing its biological and mechanical integrity.

Bernett and Stockwell in 1964 emphasized the part played in degeneration of cartilage by a reduction in permeability of the synovial membrane, and Jebens and Jones already in 1959 had found that this is due to a reduced viscosity of articular fluid [14]. Another cause of the pain is degeneration of cartilage and loss of elasticity of the subcartilaginous bone layer.

It is not easy to determine cartilage hardness *in vivo*. Radiological investigations can only detect advanced stages of the disease, and other imaging methods are similarly insufficiently sensitive and incapable of detecting the onset of the pathological process. The changes in the mechanical properties of cartilage that may occur under the influence of treatment are likewise largely unknown. *In-vitro* investigations of changes occurring in the mechanical properties of cartilage under the influence of Zeel therapy have been carried out by L. Weh and G. Fröschle [31].

The above authors determined cartilage hardness before the administration of the preparation into the joint and after 12 days of incubation with the product in Hank's isotonic solution. The culture and the medication were changed every 3 days. Cartilage incubated without any medication served as a placebo series. At the end of the incubation period, cartilage hardness was determined by an indentation method. In accordance with Radin et al. (1980), Weh and Fröschle believe that the key role is played by absorption of the subcartilaginous cortical region [32]. In cases where cartilage elasticity was reduced, as determined by smaller depth of penetration of a ball indentor, Weh et al. as already mentioned injected Zeel into the joint. However, the authors themselves realized that the investigations were associated with many technical problems. Thus, even though they did demonstrate that administration of Zeel increases penetration, an expression of a certain improvement in cartilage elasticity, they did not think that all the results can be extrapolated to the situation *in vivo*. For a more exact evaluation of the pathological changes and of the effectiveness of increasing cartilage elasticity by orally administered test medication, use is therefore often made of animal models [17]. Thus, in a study of the effects of Zeel comp. on the knee cartilage in rabbits, Stančikova et al. provoked the development of degenerative changes in the joints under investigation by severing the anterior sacral ligament. They then determined the anatomical and histological parameters and the levels of pyridinoline (a marker for decomposition of collagen) in the animals' urine. According to Sinigaglia et al. (1995) [26] and to Thompson et al. (1992) [28], the urinary pyridinoline concentration correlates significantly with the degree of destruction of cartilage and with the results of radiological studies.

9 weeks after the joint-destabilizing intervention, i.e. after complete severance of the anterior sacral ligament, Stančikova et al. inspected the knee joints in animals treated only with physiological saline. All the parameters considered in this experiment pointed to an acute course of articular degeneration in this group: roughness and thickness of the articular cartilage and the number, structure, and distribution of chondrocytes. In the group of rabbits receiving Zeel comp., on the other hand, the changes indicative of the progression of osteoarthritis were all considerably less pronounced than in the saline controls. The lower pyridinoline

levels measured in the animals' urine confirmed the chondroprotective action of Zeel. This result may therefore be taken as evidence of a beneficial action of Zeel comp. administered to human osteoarthritis patients [4].

Studying the influence of individual Zeel comp. constituents on the immune system in 1995, van der Berg [29] showed that Rhus toxicodendron and Arnica montana inhibit macrophage activity. Apart from this, it is known that Rhus toxicodendron considerably decreases the release of IL-6 and moderately increases TGF-β synthesis in human blood cell cultures. It may therefore be suggested that the above-mentioned constituents of the preparation exert an influence on the concentration of cytokines responsible for regulation of chondrocyte homeostasis.

Summing up the results of the experimental work, Zeel comp. injected intraarticularly into rabbit knees does not exert a complete chondroprotective action in joints made arthritic by severing the anterior sacral ligament. However, on the basis of morphological, histological, and biochemical investigations it may be said that it significantly reduces the damage to the articular cartilage.

The advantages of Zeel administration in degenerative joint disease have been reported in many publications describing the beneficial effects of this treatment. Thus, the product has been used in 498 patients by Wodick et al. [34] in the form of an ointment applied to the painful area under a dressing during the day or overnight, or in iontophoresis. The authors particularly mentioned its good effect on pain. Undesirable side effects – skin irritation and allergic reactions with local heat, reddening, itching, burning, and occasionally the formation of pustules and blisters – occurred in only 20 patients. Other authors compared the efficacy of Zeel P administered by iontophoresis to 10 patients and by intraarticular injection to 20 patients [35]. In the investigators' opinion, both modes of administration proved to be advantageous.

An assessment of suitability of various forms of Zeel in the treatment of arthritic joints and soft tissues has been described in a number of publications. Thus, in a study [14] Zeel was given twice weekly by injection to patients with degenerative disease of the knees (42 joints) in a dose of 2 ampoules per knee, to a total of 10 injections, and both functional and clinical improvement was achieved. Transient symptoms (in the form of intensified pain, increased joint heat, and exudation) occurred in only 2 cases, and after discontinuation of the Zeel injections for a few days they disappeared spontaneously. The treatment could then be continued. Podbiełkowski and Nejman [20] carried out a clinical analysis on 50 women with osteoarthritis of the hip, knee, and shoulder, Zeel P being administered periarticularly into the knees and shoulders and intramuscularly into the hip joints. In all study groups the results of the treatment were found to be positive. The pain in the knee, shoulder, and hip joints was alleviated and shoulder mobility increased. A complication occurred in only 1 case, in the form of increased pain in the hip.

Nahler et al. [18] compared the efficacy and the tolerability of various products in 114 patients suffering from degenerative joint disease of the knees. The group was divided into two subgroups of 57 individuals. In one subgroup, the patients received 10 injections of Zeel comp. each over the course of 5 weeks (2 injections of 2 ml per week) and in the other subgroup 5 injections of Hyalart (2 ml once a week). Both

products were found to be effective. The side effect reported most frequently was the appearance of local symptoms of joint inflammation: these occurred in 6 patients receiving Zeel comp. and in 13 receiving Hyalart.

Weiser and Metelmann [32] conducted clinical trials in 1845 patients having osteoarthritis of the knee and treated with Zeel P solution given by injection. Each patient was injected in the knee with 1 ampoule of Zeel P on average twice a week for 4 to 5 weeks. Towards the end of this treatment, 93.1% assessed the therapy positively – as satisfactory, good, or very good. In the course of the treatment, 69 patients experienced side effects, all in the form of symptoms of inflammation: pain, heat, and swelling in the knee and reddening of the skin. In 24 cases these symptoms regressed spontaneously after a break in the treatment, and in the remaining patients application of ice packs or oral administration of NSAIDs or steroids proved to be sufficient. Puncture of the joint to withdraw exudation was carried out in 36 cases.

Intraarticular injections are always associated with a greater risk of complications compared with non-invasive treatment. The authors suggest combining the test product with an anesthetic, alleviating the painful reactions and exerting a slight antiinflammatory effect.

What is not clear is whether the undesirable side effects are a reaction to the product's action as such or only to the method of its administration. The authors cite Bernau et al. (1985), who believe that even when very thin needles are used for the injection, it is difficult to avoid displacement of a skin fragment into the joint. The skin cells may then provoke an inflammatory reaction by the formation of interleukin 1. This has also been mentioned by Dowd et al. in 1988 (cited after Weiser [32]). Local inflammatory symptoms may therefore appear as a result of this joint irritation and need not in all cases be due to the injected material itself. Good results of osteoarthritis therapy with Zeel P have been reported in recent years by Weiser and Metelmann and also by Hieber (1971), Kasanmascheff (1971), Schlufer (1975), Karch and Lasagna (1975), and by others. Even injections close to the affected joints in the cervical and lumbar spine clearly alleviated pain and improved vertebral joint function in 82% of the cases [21].

Taking into account the investigators' experience so far and also our own results, it should be concluded that Zeel in its various forms exerts a distinct antiinflammatory and analgesic action and also has a slight antiexudative activity. In addition to this, it corrects synovial membrane metabolism and regulates the composition of the synovial fluid. This improves the biological state of the cartilage and in some cases makes it possible to arrest or at least slow down the progression of the degeneration processes. Treatment with Zeel is safe and easy to apply. The adverse reactions are moderate, not dangerous, and rare.

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